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10/796,925	03/10/2004	Wumin Li	AM 101333	3270

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EXAMINER	
TONGUE, LAKIA J	
ART UNIT	PAPER NUMBER
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/796,925	LI ET AL.	
	Examiner	Art Unit	
	Lakia J. Tongue	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on December 1, 2006 is acknowledged. Claims 22 and 23 are pending and currently under examination.

Rejections Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. The rejection of claims 22 and 23 under 35 U.S.C. 103(a) as being unpatentable over Doyle et al (U.S. Patent 5,965,128), in view of Clancy et al (U.S. 2004/0057965 A1), and further in view of the SIGMA Catalog (Biochemicals and Reagents for life science, 2000-2001, Adjuvants, pages 1472) is maintained for the reasons set forth in the previous Office action.

Applicant argues that:

1) Doyle et al do not imply that probiotic bacteria can act in any way shape or form as a vaccine to reduce shedding.

2) The practitioner would have no reasonable expectation of success in reducing shedding of *E. coli* O157:H7 through the administration of Applicants' vaccine composition and the stimulation of a strong immune response.

3) Clancy et al. teach that the antigen is derived from a bacterium, a fungus or a virus, but only describes those antigens that are respiratory tract pathogens

4) Clancy et al. do not describe, exemplify or suggest any antigens that colonize the intestinal tract let alone *E. coli* O157:H7.

5) Since Clancy et al. do not suggest a specific antigen such as the metabolizable oil in a respiratory tract vaccine, such a bare and limited disclosure certainly does not imply using the metabolizable oil adjuvant elsewhere.

6) A generic list of adjuvants from one chemical supplier's catalog does not provide any teaching of which particular adjuvant can be used in concert with which antigen for what results.

7) The unique metabolizable oil adjuvant in Applicants' vaccine composition provides beneficial and unexpected results over those seen with conventional adjuvants that are not taught in the art.

Applicant's arguments have been fully considered and deemed non-persuasive.

The instant invention is drawn to a method for reducing shedding of *E. coli* O157:H7 in an animal which comprises administering to the animal an effective amount of a vaccine composition containing *E. coli* O157:H7, wherein the vaccine composition comprises inactivated or killed whole *E. coli* O157:H7, a metabolizable oil adjuvant and optionally a pharmaceutically acceptable carrier.

With regard to Points 1-7, in response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce

the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Further, with regard to Point 1, Doyle et al. specifically teach a method for reducing or eliminating *E. coli* O157:H7 by administering an effective amount of dominant probiotic bacteria thereby reducing carriage and fecal shedding of *E. coli* O157:H7 (see column 2, lines 61-67). Moreover, the term "probiotic" in this instance is bacteria having the property of preventing the establishment of *E. coli* O157:H7 in a ruminant animal (see column 2, lines 32-36).

With regard to Point 2, the combination of references teach the claimed method of administering to the animal an effective amount of a vaccine composition containing *E. coli* O157:H7, wherein the vaccine composition comprises inactivated or killed whole *E. coli* O157:H7, a metabolizable oil adjuvant and optionally a pharmaceutically acceptable carrier as claimed and therefore necessarily would be effective in reducing the shedding of *E. coli* O157:H7 in an animal.

With regard to Point 3, Clancy et al. does not just describe respiratory tract vaccines. Clancy et al. teach compositions and vaccines, which can be applied to any potential mucosal pathogen and any mucosal surface, including but not limited to the intestinal tract. Further, Clancy et al. supports administering whole inactivated bacteria together with an adjuvant for the treatment of an intestinal infection. Finally, Doyle et al.

specifically disclose their method reduces "carriage and fecal shedding of *E. coli* O157: H7" (see column 2, lines 65-67).

With regard to Point 4, while Doyle et al. explicitly states that *E. coli* O157:H7 does not adhere to or infect cattle, Doyle et al. does teach that the primary sites of *E. coli* O157:H7 localization in calves are the rumen and colon. The rumen appears to be the most important site for long-term carriage of *E. coli* O157:H7, and may serve as the source of bacteria found in the colon (see column 1, lines 59-63).

With regard to Points 5 and 6, Clancy et al. teach known conventional and suitable pharmaceutical adjuvants should be included when preparing suitable formulations and would be well known to those skilled in the art. The Sigma catalog teaches a list of known conventional and suitable pharmaceutical adjuvants. Since Clancy et al. teach that any known conventional and suitable pharmaceutical adjuvant can be used it would have been obvious to use a metabolizable oil adjuvant from the Sigma catalog.

With regard to Point 7, Applicant's assertion of unexpected results, Applicant has failed to provide evidence supporting said assertion. The MPEP states:

716.02(b) Burden on Applicant
BURDEN ON APPLICANT TO ESTABLISH RESULTS ARE UNEXPECTED AND SIGNIFICANT
The evidence relied up should establish "that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance." Ex parte Gelles, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992) (Mere conclusions in appellants' brief that the claimed polymer had an unexpectedly increased impact strength "are not entitled to the weight of conclusions accompanying the evidence, either in the specification or in a declaration."); Ex parte C, 27 USPQ2d 1492 (Bd. Pat. App. & Inter. 1992) (Applicant alleged unexpected results with regard to the claimed soybean plant, however there was no basis for judging the practical significance of data

with regard to maturity date, flowering date, flower color, or height of the plant.). See also In re Nolan, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977) and In re Eli Lilly, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) as discussed in MPEP § 716.02(c).

APPLICANTS HAVE BURDEN OF EXPLAINING PROFFERED DATA

"[A]ppellants have the burden of explaining the data in any declaration they proffer as evidence of non-obviousness." Ex parte Ishizaka, 24 USPQ2d 1621, 1624 (Bd. Pat. App. & Inter. 1992).

DIRECT AND INDIRECT COMPARATIVE TESTS ARE PROBATIVE OF NONOBVIOUSNESS

Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. See In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) and MPEP § 716.02(d) - § 716.02(e). See In re Blondel, 499 F.2d 1311, 1317, 182 USPQ 294, 298 (CCPA 1974) and In re Fouche, 439 F.2d 1237, 1241-42, 169 USPQ 429, 433 (CCPA 1971) for examples of cases where indirect comparative testing was found sufficient to rebut a prima facie case of obviousness. The patentability of an intermediate may be established by unexpected properties of an end product "when one of ordinary skill in the art would reasonably ascribe to a claimed intermediate the contributing cause' for such an unexpectedly superior activity or property." In re Magerlein, 602 F.2d 366, 373, 202 USPQ 473, 479 (CCPA 1979). "In order to establish that the claimed intermediate is a contributing cause' of the unexpectedly superior activity or property of an end product, an applicant must identify the cause of the unexpectedly superior activity or property (compared to the prior art) in the end product and establish a nexus for that cause between the intermediate and the end product." Id. at 479.

Additionally, 716.01(c) Probative Value of Objective Evidence TO BE OF PROBATIVE VALUE, ANY OBJECTIVE EVIDENCE SHOULD BE SUPPORTED BY ACTUAL PROOF

Objective evidence which must be factually supported by an appropriate affidavit or declaration to be of probative value includes evidence of unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. See, for example, In re De Blauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984) ("It is well settled that unexpected results must be established by factual evidence." "[A]ppellants have not presented any experimental data showing that prior heat-shrinkable articles split. Due to the absence of tests comparing appellant's heat shrinkable articles with those of the closest prior art, we conclude that appellant's assertions of unexpected results constitute mere argument."). See also In re Lindner, 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972); Ex parte George, 21 USPQ2d 1058 (Bd. Pat. App. & Inter. 1991).

ATTORNEY ARGUMENTS CANNOT TAKE THE PLACE OF EVIDENCE

The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.

As previously presented, Doyle et al teaches a method for reducing shedding of *E. coli* O157:H7 in an animal by administering an effective amount of *E. coli* O157:H7 to infected animals (column 5, lines 58-61). Moreover, Doyle et al teaches the administration of a strain or combination of probiotic bacteria (column 2, lines 61-67). Doyle et al does not teach a vaccine specifically comprising inactivated or killed whole *E. coli* O157:H7, a metabolizable oil adjuvant or an effective amount of *Lactobacillus acidophilus.*

Clancy et al teaches a method for the treatment of mucosal infections which comprises administering compositions to any potential surface pathogen (i.e. the intestinal tract; 0015, 0017). Clancy et al teaches that the mucosally administrable compositions comprises one or more antigens derived from at least one microorganism which is capable of causing infection at a mucosal surface and a probiotic. The microorganism is a whole killed, live or live attenuated microorganism (0005-6). Clancy et al teaches that an affective amount is from about $1x10^8$ to about $1x10^{12}$ (0025). Moreover, the composition may be combined with known pharmaceutically acceptable carriers, solvents and excipients (0008). A preferred probiotic to be used in the composition is *Lactobacillus acidophilus* among others (0009). Lastly, Clancy et al teaches that a range of suitable pharmaceutical adjuvants can be used and would be

well known to those skilled in the field of pharmaceutical formulations. Clancy et al does not specifically teach a metabolizable oil adjuvant.

The Sigma catalog teaches commonly used adjuvants, which include but are not limited to squalene, which is a metabolizable oil (1472).

Doyle et al and Clancy et al teach analogous inventions related to methods for treating infections of the intestinal tract by administering a composition, which comprises an antigen, a probiotic and optionally a pharmaceutical carrier. It would have been *prima facie* obvious to a person having ordinary skill in the art at the time the invention was made to modify the invention of Doyle et al with the teaching of Clancy et al because Clancy et al teaches combining whole killed microorganism together with an adjuvant and a probiotic. Moreover, it would be obvious to modify the invention of Doyle et al and Clancy et al with the Sigma catalog because the Sigma catalog teaches commonly used commercial adjuvants that are used to enhance an immune response. It would have been expected, barring evidence to the contrary, that the method would be effective in reducing the shedding of *E. coli* O157:H7.

2. The rejection of claims 22 and 23 under 35 U.S.C. 103(a) as being unpatentable over Doyle et al (U.S. Patent 5,965,128), in view of Clancy et al (U.S. 2004/0057965 A1), and further in view of the SIGMA Catalog (Biochemicals and Reagents for life science, 2000-2001, Adjuvants, 1472) as applied to claims 22 and 23 above, and further in view of Molly et al (U.S. 2005/0084500 A1) is maintained for the reasons set forth in the previous Office action.

Applicant argues that:

1) Molly et al. purely suggest that neomycin be used in combination with the fungus to improve the gastrointestinal microbial ecosystem by suppressing pathogens on the gastrointestinal tract of the animals.

2) There are no specific formulations or examples that contain neomycin.

3) It is plain to see that Molly et al. do not promote the use of an animal feed antibiotic such as neomycin in the absence of fungus as it will have an adverse effect on the animal.

Claims 22 and 23 is drawn to a method for reducing shedding of *E. coli* O157:H7 in an animal which comprises administering to the animal an effective amount of a vaccine composition containing *E. coli* O157:H7, wherein the vaccine composition comprises inactivated or killed whole *E. coli* O157:H7, a metabolizable oil adjuvant, optionally a pharmaceutically acceptable carrier and further comprising a neomycin medicated feed supplement to animals.

With regard to Points 1 and 2, the instant claim recites open claim language and thus does not exclude other materials (i.e. fungus) from being present in the claimed composition. Moreover, the fact that there are no specific formulations or examples that contain neomycin alone is irrelevant. Lastly, said fungus is edible and serves as an added supplement to the medicated feed.

With regard to Point 3, Applicant is reminded that the rejection is an obviousness rejection over the combination of said references. Further, Molly et al teach a method of administering a composition, which comprises an animal feed antibiotic (neomycin) for

the improvement of intestinal function against enteric pathogens and would be suitable for the suppression of enteric pathogens like *E. coli* (see paragraph 0059).

As previously presented the teachings of Doyle et al, in view of Clancy et al, and further in view of SIGMA have been taught above. Neither of them teaches administering a neomycin medicated feed supplement to an animal.

Molly et al teaches a method for improving the gastrointestinal tract by enumerating enteric pathogens such as *Escherichia* (0059). The method is accomplished by administering useful compositions, which comprises an animal feed antibiotic including but not limited to neomycin (0036). Moreover, Molly et al teaches that the composition can be suitable for the improvement of intestinal function and when fed to dairy animals such as cows, goats and ewes can improve milk production (0047).

In view of all of the above, it would have been *prima facie* obvious to a person having ordinary skill in the art at the time the invention was made to modify the invention of Doyle et al with the teachings of Clancy et al and with the teachings of the Sigma catalog with the teachings of Molly et al because the composition of Molly et al helps with the improvement of nutrient replenishment digestion and absorption as well as disease prevention. It would have been expected, barring evidence to the contrary, that the method would be effective in reducing the shedding of *E. coli* O157:H7.

3. The rejection of claim 22 under 35 U.S.C. 103(a) as being unpatentable over Johnson et al (Effect of dairy calves with an inactivated *E. coli* O157:H7 bacterin on shedding of *E. coli* O157:H7, 1999; Abstract 40 aP), in view of SIGMA (Biochemicals

and Reagents for life science, 2000-2001, Adjuvants, 1472) is maintained for the reasons set forth in the previous Office action.

Applicant argues that:

1) Johnson et al. did not significantly reduce the shedding of *E. coli* O157:H7 in the feces of cattle.

2) Johnson et al. disclose a totally different vaccine composition containing inactivated *E. coli* O157:H7, inactivated verotoxin 2 and intimin O157, which does not suggest Applicants' efficacious vaccine formulation.

3) The practitioner would have no reasonable expectation of success in reducing shedding of *E. coli* O157:H7 by a vaccination approach.

Claim 22 is drawn to a method for reducing shedding of *E. coli* O157:H7 in an animal which comprises administering to the animal an effective amount of a vaccine composition containing *E. coli* O157:H7, wherein the vaccine composition comprises inactivated or killed whole *E. coli* O157:H7, a metabolizable oil adjuvant and optionally a pharmaceutically acceptable carrier.

With regard to Points 1 and 3, the degree to which shedding is to be reduced is irrelevant. Moreover, contrary to Applicant's argument, Johnson et al. teach that shedding of the organism by most calves in each group fell to <50 CFU/g of feces within 2-3 weeks of challenge, thus meeting the limitation of reducing shedding of *E. coli* O157:H7 in an animal and meeting the requirement of a reasonable expectation of success.

With regard to Point 2, the instant claim recite open claim language and thus does not exclude other materials (i.e. inactivated verotoxin 2 and intimin O157) from being present in the claimed composition.

As previously presented, Johnson et al teaches a method of vaccination calves with 10^{10} CFU of inactivated *E. coli* O157:H7 bacterin to reduce the shedding of the organism. Johnson et al does not teach a metabolizable oil adjuvant or the optional pharmaceutically acceptable carrier.

The Sigma catalog teaches commonly used adjuvants include but are limited to squalene, which is a metabolizable oil (1472).

It would have been *prima facie* obvious to a person having ordinary skill in the art at the time the invention was made to modify the invention of Johnson et al with the teaching the Sigma catalog because it is obvious to add an adjuvant to vaccine because they are used to enhance an immune response and the Sigma catalog teaches commonly used commercial adjuvants. It would have been expected, barring evidence to the contrary, that the method would be effective in reducing the shedding of *E. coli* O157:H7. Limitations such as "optionally" are being viewed as a limitations that may or may not be present in the prior art.

Conclusion

4. No claim is allowed.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakia J. Tongue whose telephone number is 571-272-2921. The examiner can normally be reached on Monday-Friday 8-5:30.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO

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LJT

2/27/07

ROBERT A. ZEMAN
PRIMARY EXAMINER